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[Reprint from INTERSTATE MEDICAL JOURNAL, Vol. XVII., No. 6, 1910.]

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THE CANCER PROBLEM.*

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We can approach the cancer problem from the standpoint of the physician who is concerned with its practical aspects, who wishes to learn how to prevent and how to cure cancer, and by what means it destroys the health of the patient, and we can also consider it from the point of view of the investigator, the biologist, who is concerned with the phenomena of life. The latter is deeply interested in the problem of tumors, and especially of cancer. From a study of these phenomena he hopes to gain a deeper insight into one of the most important attributes of living matter, into its power to grow and to proliferate.

In this necessarily brief and very incomplete sketch, I shall try to consider the cancer problem from both these points of view, at the same time limiting myself to a few only of the many sides of this problem.

Let us, first, for a short time consider the problem from the point of view of the physician.

Every organ of the human body can be attacked by cancer, but certain organs are much more frequently affected than others. At first there is a localized swelling that enlarges. Frequently the cancer breaks through the surface of the organ, and a part of the tissue may break down. Sooner or later other parts of the body, especially the lymph glands, the liver, and lungs, become the seat of similar tumors, and at last the patient dies in an emaciated condition.

Cancer is not restricted to any special race of men; it is found in all races, but with very unequal frequency. Thus, the aborigines in tropical Africa are rarely affected; the same holds good of the natives of all the tropical countries. Even in different parts of Europe cancer occurs with unequal frequency. Thus in the countries situated around the Mediterranean and in Hungary cancer is found less frequently than for instance in Switzerland and in Denmark, where cancer is more common than anywhere else in Europe.

The question arises whether those differences in the cancer morbidity are primarily questions of race or whether they are due to the external conditions under which the races live. This question has not yet been answered satisfactorily, but it seems to me that America, where immigration of different races has taken place, might be favorable for such a study. Inasmuch as in the American negro cancer is more frequent than it is among the African negroes, it might appear as though environment and conditions of life were the principal factors concerned; it is very probable indeed that these factors are of great importance. On the other hand, we have to consider that inter-mixing of the races has taken place, so that in this case the action of the race factor cannot be entirely excluded.

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*Read before the Society of Biological Research Workers of Washington, D. C., on April 9, 1910. It has been the aim of the writer to explain the technical terms used, whenever feasible, in consideration of the character of the audience, which included botanists and chemists.

References to previous researches of the writer and of other investigators, on which the conclusions presented in this paper are based, can be found in other communications of the author and have been omitted here for the sake of briefness. Some of the facts mentioned have not yet been published elsewhere.

We also find that in different countries different organs are attacked with unequal frequency, and this is due certainly to a great extent to the different habits that prevail. Cancer of the lip is found to be frequent only in people that smoke; and, in a similar way, cancer of other organs can to some extent be accounted for by considering the different habits of various peoples.

We find other variations in the incidence of cancer, namely, in regard to the time factor. In all countries in which statistical records of all the deaths occurring are kept, a constant definite increase in the frequency of cancer has been noted. In the United States 90 persons per million inhabitants died from cancer in 1850, while in 1900 the death rate per million inhabitants was 430. In Germany there was from 1876 to 1895 an increase in the rate of death due to cancer of approximately 115 per cent., while the increase in population in the same period amounted to only 23 per cent. A similar increase has been observed in other countries.

This increase is the more surprising, because the mortality of certain other diseases, especially tuberculosis and the infectious diseases in the restricted sense of the word, is constantly decreasing. This increase is, however, by some investigators interpreted as only apparent, and is explained as mainly due to a better recognition of the disease—an interpretation against which some serious objections can be raised. However that may be, there can be no doubt as to the wide distribution and the great importance of this disease.

During the greater part of the nineteenth century the study of cancer consisted mainly in a microscopic study of the various tumors, of their mode of origin, and of the paths along which the cancer spread in the body, and these studies led to some very interesting observations. Some preliminary explanation concerning certain technical terms may first be given.

Our body consists of cells, and certain varieties of cells form larger combinations, which we call tissues. The morphological and chemical character of the cells of different tissues is different. Those cells which cover the skin and certain internal organs are called epithelia and the other cells that are situated beneath the epithelial lining and that connect the various tissues are called connective tissue. Normally, the arrangement of different tissues and the boundary line between them is quite definite. In studying early stages of cancer, cancer of the skin, for instance, we see that such a definite arrangement is lost, and that the epithelial cells which form the outer lining of the skin begin to grow down into the underlying layer of connective tissue. This downgrowth is usually limited to a very small, localized area. While in normal skin the line of demarcation between the epithelium and the underlying connective tissue is sharp, in the case of the beginning cancer both kinds of tissue are intermixed, the epithelium penetrating downward into the connective tissue; secondarily, the surrounding connective tissue likewise begins to proliferate, and thus a swelling, a tumor-like mass, may be produced. The growing epithelial cells do not respect any opposing tissue. They are able to destroy cartilage and bone and can penetrate the wall of the lymph channels and of the blood-vessels. With the circulating blood or lymph they may be carried into different parts of the body, into a lymph-gland or into the liver, for instance. Here the tumor cells are retained and frequently begin again to proliferate, forming a tumor similar to the one found at the primary seat. At first the cancer cells grow inside the lumen of the lymph or blood channel, but very soon they break through their wall to the outside and then a growth takes place in the organ proper. Such a secondary growth is called a metastatic tumor.

We see that tumor growth depends on the activity of those cells which had been transformed into cancer cells in a restricted area and later spread into other parts of the body; it is quite different in infectious diseases, in which, not the body cells, but the microorganisms, spread in the body and cause new cells at different places to proliferate. Usually cancer takes its origin at one place of the body only; but in some cases it may happen that a simultaneous proliferation takes place at different parts of the body or at different parts of an organ; for instance, it occasionally happens that multiple areas of the outer skin become cancerous at the same time. In other cases cancer may simultaneously occur in different organs of the body.

The same changes that I have just described in the case of cancer of the skin may take place in almost any other tissue, and we designate the different tumors according to the tissues from which they originate. Thus, a cancer taking its origin from the epithelial tissue is called a carcinoma, and a cancer originating in the connective tissue is called a sarcoma. On the whole, a tumor preserves its morphological and chemical characters throughout; but certain variations in the character of cells have been observed, and to some very marked variations we shall later have an opportunity to refer.

Such were the principal results obtained through the microscopic study of human cancer as it was practiced during the second half of the nineteenth century. On the whole, the data brought forth through a continued microscopic study taught us to differentiate between various kinds of tumors, according to the variety of tissues in which the proliferation started. But the number of variable factors in such phenomena of growth is very great, and by mere morphological observation it was found impossible to eliminate these variable factors. Thus an exact solution of the problem being impossible, a period set in in which hypothetical speculations acted as a substitute for real facts. This epoch, which we have not quite overcome, has been productive of a legion of hypothetical explanations which, in the large majority, have not been well founded, and will merely retain some historical interest. They are frequently based on a limited number of histological observations and are therefore entirely inadequate to do justice to a very complex reality.

In order to eliminate those variable factors as much as possible it was necessary to use the same methods that are employed for this purpose in other sciences—we had to resort to experiment. In order to carry out such experiments it was necessary to recur to animal tumors.

Tumors have been observed to occur in the various classes of vertebrates, but their frequency varies very much according to the species of animals. To mention some examples, tumors are extremely rare in guinea-pigs, and almost as rare in rabbits; they are very common in dogs, white mice, and white rats. It has been suggested that animals living in a wild condition are less apt to be affected by tumors than domesticated races. This, however, has not yet been conclusively proved. Thus it seems that tumors are relatively common in the grey rat and also in the grey mouse, and tumors have also been found in wild animals kept in zoological gardens. The varieties of tumors found in animals are identical with those observed in man; but it is noteworthy that certain species of animals have tumors that are more or less characteristic for the species to which they belong. Thus, in the white rat connective tissue cancer is relatively common, while in the white mouse epithelial cancer of the mammary gland predominates; in cattle in the United States carcinoma of the inner angle of the eye is the typical form of cancer, while in Europe this kind of cancer seems to be rare or to occur not at all.

Cancer has also been observed among birds, reptiles, amphibia and fish; but in cold blooded animals tumors are on the whole very rare.

In order to get a deeper insight into the growth of tumors it was necessary to undertake the experimental study of animal tumors. Such a study was rendered feasible through the discovery that under certain conditions it is possible to transmit a tumor from one animal to another. This can be accomplished very easily in mice and rats, and the majority of experiments have been carried out in those rodents. But tumors can also be propagated in other animals. In order to transmit a cancer from one animal to another we have to inoculate a very small particle of the tumor under the skin of the mouse or rat, and if such an inoculation is successful the tumor will begin to grow and become visible to the naked eye in a period of time that varies between one week and several months, according to the tumor used. The rapidity of growth also varies in different tumors. The process of inoculation is hardly more painful than a subcutaneous injection which the physician frequently makes for therapeutic purposes, and the subsequent growth of the tumor is not connected with any pain sensation. When the tumor has grown to any considerable size the mouse is usually chloroformed. What takes place after the inoculation of a very small fragment of tumor? The cells in the centre of the piece usually die, but the peripheral cells, which are nourished by the fluids of the host, remain alive, and they soon begin to divide by mitosis and give rise to the new tumor formation. It is absolutely necessary to inoculate living tumor cells into the other animal, otherwise the results will be negative. The number of cells inoculated, however, may be very small and one single cell injected may be sufficient in certain cases to make the inoculation successful. In this respect the transmission of cancer differs, therefore, considerably from the transmission of common infectious diseases, in which it is necessary to transfer not the body cells but merely the microorganisms from one organism to another. In cancer, cells must be transmitted. Thus it becomes readily understandable why usually it is not possible to make the tumor of one species grow in another species for any length of time. It is, for instance, not possible to make a human cancer or cancer of a dog grow in a mouse, nor is it possible to make the tumor of a mouse grow in a guinea-pig. Even in relatively nearly related species tumors do not grow. Thus the tumors of a rat do not grow in a mouse for any length of time; although for a short period they may grow, but then they rapidly retrograde and disappear. This behavior of tumors can easily be understood if we consider that transplantation of tumor means the transmission of the tumor cells; and these tumor cells retain all the characters of the species which the normal cells of an organism possess. We must assume that the chemical structure of the proteids of animals belonging to one species differs from the chemical structure of the proteids of animals belonging to another species, and that these specific proteids are adapted to certain substances circulating in the body fluids, much as a key is adapted to a certain keyhole. Each tissue finds, therefore, the nourishing material in the animals of the same, but not of other, species. Thus, if we transplant skin from one guinea-pig into another guinea-pig, it may live a very long time, perhaps permanently; but if we transplant that same skin into a rabbit or into a pigeon, the skin lives, and may even show a small increase in the number of cells for a few days, but after this brief preliminary period it invariably dies. Cancer cells behave in this respect like ordinary tissue cells. Different varieties of cancer are, however, not equally sensitive to changes in hosts. Thus a certain sarcoma found in dogs can be transmitted even to the fox, which represents a different, though closely related, species. On the other hand, carcinomata of the mouse have been found to be very sensitive to differences in the character of the host. A tumor, for instance, which has originated in an American strain of white mice grows with very much greater difficulty in white mice that have been bred in Europe.

We can easily understand such differences if we consider the probability that the chemical composition of the protoplasm of the cells is different in different strains of the same species, that such differences in the character of the cells determine a corresponding difference in the circulating food-stuffs that nourish the cells, and that the difference in the food-stuffs renders the growth of ordinary cells, and especially of tumor cells, more difficult. Very frequently the specificity in the adaptation between body cells and nourishing body fluids is still more pronounced, and the majority of tumors cannot be transplanted successfully, even into animals of the same species and the same strain. But such tumors as do not grow in other animals of the same species and the same strain may grow if they are transplanted into the same individual in which the tumor had originated; this shows a still finer adaptation between tumor cells and the body juices, and it agrees very well with a recent important discovery of von Dungern's, according to which it is possible to distinguish by biochemical means even between certain individuals of the same species. Individuals of the same species differ, therefore, in their chemical structure and react, therefore, in a different way against their own transplanted cells and the transplanted cells of another individual of the same species.

Let us now assume that we have succeeded in transplanting tumor cells into a number of individuals of the same species. What becomes of these tumor cells after they have lived for some time in their new hosts? Does their power of proliferation now gradually decrease, and do they die simultaneously with the individual in which the tumor originated? Experiments have conclusively shown that this is not the case. From the second generation such tumor cells can be transferred into a third generation and into a fourth, and so on apparently indefinitely. This holds good for connective tissue tumors as well as for epithelial tumors, both have been kept alive in other individuals for a long period of time; they survived the animal in which the cancer had originated. Thus one tumor found in Copenhagen has been kept alive through a period of more than eight years and during that time the cells continued to propagate at an extraordinary rate. All other tumors that can be transplanted behave in the same way. This is a fact of the greatest biological significance. In order to appreciate its importance we must refer to some of the fundamental conceptions of biology. In the multicellular animals, the Metazoa, of which the vertebrates form one group, we distinguish two kinds of cells, the germ cells, ova and spermatozoa, which propagate the species, and all the other cells, which are called somatic cells. The cells of the skin, the muscle, nerve cells, and so on, all are somatic cells. Now we know that the somatic cells die with the individual of which they form a part, while the germ cells do not necessarily die with the rest of the body, but have the power to give origin to new individuals indefinitely. While, therefore, the germ cells possess the potentiality of immortality, the somatic cells are supposed to be hopelessly mortal. In regard to the unicellular animals, the Protozoa, Weismann claimed for them potential immortality, inasmuch as one individual divides directly into others to which it transmits its protoplasm, a process which safeguards the continuity of their body. Later, however, other investigators, like Maupas, Hertwig, Calkins, and others, came to different conclusions. They noticed that in propagating a certain strain of Protozoa, as for instance Paramœcia, these organisms do not retain their vitality constantly, but that after a period of active division, the Protozoa begin to show signs of deterioration, and without conjugation of two individuals the strain is in danger of dying out. These later investigators believed, therefore, that the Protozoa are subject to death in the same way as the Metazoa and that only a certain part of their protoplasm which conjugates with part of the protoplasm of another individual of the same race, escapes death and is immortal; this latter part corresponds to the germ protoplasm of the Metazoa, while the rest of the protoplasm that dies they regard as the homologon of the somatic portion of the metazoan body. If we analyze somewhat more closely the arguments used in favor of the conception that the somatic cells of the Metazoa are necessarily mortal, we find that they are based on hypothetical considerations and that no convincing proof has been given that the somatic cells cannot live indefinitely. The experimental investigation of tumors brought forth facts that point very strongly to the converse conclusion, namely, that, if not all, at least very many of the somatic cells are potentially immortal in the same sense as is generally recognized in the case of the germ cells. It seems to me difficult to conceive of any other conclusion, if we find that the tumor cells, which are merely, a special kind of somatic cell, propagate indefinitely through periods of years long after disintegration has set in in the body of which the mother cells that gave origin to the tumor elements formed an integral part, and especially if we consider that at the present time there is not yet the least sign noticeable of a decreasing energy of growth of these tumor cells. Furthermore, this conclusion holds good of connective tissue as well as of epithelial cells, and it is probably equally true in the case of cartilage and certain other cells.

Under the conditions under which animals actually exist, their somatic cells do indeed cease to live at the time when the nervous system and the heart discontinue their activity. This, however, may be merely the result of unfavorable environmental conditions that exist in the body at the time of the death of the animal, and if transplanted from the aged or dying into a young individual of the same species the tissues in all probability would continue to live. To the same conclusion recent experiments that concern the life of Protozoa point. It appears that in this case also the period of depression and death noted by former investigators, periods of depression from which recovery is sometimes possible by means of conjugation, are not inherent in the structure of the protoplasm of the unicellular organism, but are caused by unfavorable environmental conditions, by lack of proper food, and especially by lack of the proper variation in the nourishment. To the older view we can, therefore, oppose, on the basis of important evidence, the other conception that many somatic cells, as well as many Protozoa, have the potentiality of immortality, and that in the service of the mortal individual animal these somatic cells sacrifice their immortality.

We say that the tumor cells can be propagated apparently indefinitely from generation to generation. We have said also that in the course of this propagation no decrease in the energy of growth need take place.

Does this indicate that the energy of growth is a non-variable factor, remaining constant under all conditions? This is not the case. The energy of tumor growth can be experimentally changed; it can be increased and can be decreased. An increase of the energy of tumor growth takes place almost immediately if we transplant a primary tumor, a tumor that originated spontaneously in a certain animal, into another individual. In the course of the first, second, and sometimes also the third, generation, the tumor gains in rapidity of growth often quite markedly. We see, therefore, that the original tumor grows relatively slowly, and that in the animal in which all the conditions were present that made possible the conversion of normal tissue cells into tumor cells, the energy of growth of these tumor cells is lower than in other animals in which no special, favorable conditions existed for the formation of the tumors. Thus, the curve representing the energy of tumor growth shows an optimum after the first few generations, after which it reamins approximately constant, although variations may occur, which, however, are very soon equalized. What is the cause of this typical variation taking place in the course of the first transplantation? Is it due to a restraining influence exerted by the animal originally affected with the tumor growth, a restraining influence that is lacking in other animals of the same species? This is not the correct explanation; it can be shown that we are able to stimulate the proliferative power of the tumor cells without transplanting them into another animal merely by excising a piece of the cancer, and placing this cut out piece in another part of the same individual, or even by pulling a thread through a tumor. Such experimental interferences act, therefore, as formative or growth stimuli, increasing the proliferative process of the tumor. This fact explains an observation that surgeons have frequently made. It has been noted that if operative excisions of a tumor have been incomplete and if from the very small remnant of the tumor a new cancer begins to grow this so-called recurrent cancer frequently proliferates much more rapidly than the first tumor. In this case also the proliferative energy of the tumor cells has, therefore, been stimulated through external means. On the other hand it is possible experimentally to decrease the virulence of tumor cells, to make rapidly growing cancer grow very slowly after transplantation. This can be accomplished in the following way: After excising a piece of tumor we expose the tumor in a test tube in the thermostat to a temperature slightly above the body temperature, for instance 44°C. According to the length of time during which the tumor tissue is exposed to that temperature, the energy of growth generally decreases; exposure of from 10 to 20 minutes changes its proliferative power very little or not at all—but heating it for 25 minutes depresses its growth somewhat; an exposure of 35 minutes has a very distinctive influence; after heating it for 45 minutes the tumor growth becomes slight and is still more markedly decreased if we heat it during one hour. If we transplant into animals of the suitable species particles of cancer that have thus been exposed, we can readily recognize the decrease in the virulence of the cancer that has been subjected to heating before inoculation.

Exposure to the action of certain chemicals, such as glycerine and very weak solutions of potassium cyanide, act in a similar manner. These experiments and observations are of very great biological interest and importance. They clearly show that if you affect a body cell in such a way as to retard its cell division, a hereditary transmission through many generations of cells takes place, and that not only the cells directly affected, but also their daughter cells, and the third and the fourth generation of cells and so on through many generations, continue to divide more slowly. If the exposure has been too long or too severe, the tumor cells may die after a limited number of divisions; but if the cancer cells begin, though slowly, to propagate, usually a recovery takes place after many cell divisions, and if we continue to transplant such a tumor into other animals the cancer may regain its old virulence. This appears to be very important from a biological point of view. It clearly proves that the injuries to which somatic cells invariably are exposed during the life of the individual of which they form a part, do not necessarily lead to the ultimate death of these cells, as has been assumed by some investigators, but that certain mechanisms exist which, inside of very wide limits, bring about a recovery of the energy of growth and of other vital functions, even without rejuvenation having taken place through a conjugation, as is held by various investigators to be necessary in the case of Protozoa. It seems very plausible that a similar mechanism exists also in the case of Protozoa and that the latter succumb only to a constantly accumulating effect of injuries. These facts, therefore, give a further support to the hypothesis mentioned before, that ordinary tissue cells, as well as tumor cells, may be immortal.

Here again we find that connective tissue and epithelial cancer cells behave in approximately the same manner, confirming thus the fundamental similarity in the physiological properties of various somatic cells independently of their genetic relationship.

If we now expose the cancer cells to the same temperature for a still larger period of time or if we increase the temperature or the concentration of the poisonous chemical substances, the cells die altogether and no growth results after transplantation of particles of cancer thus treated. To the influence of cold, cancer cells are very much more resistant. They can be kept for a relatively long period of time at the temperature of melting ice without losing their power to grow after inoculation into an animal. They can withstand even a temperature considerably below the freezing point without being injured to any very marked degree. These properties, however, are not characteristic of tumor cells, but so far as our present investigations permit of any definite statement they are common to cancer cells, to many normal tissues, and even to unicellular organisms.

If we study carefully the growth of such tumors of experimentally decreased virulence, we notice that a certain number of these cancers grow for a certain period of time, and then, instead of continuing to grow as cancers usually do, their proliferation ceases at first, and they begin to disappear, until within a relatively short period of time they disappear entirely and nothing indicates that a cancer ever had grown in such an animal. Similar retrogressions occur occasionally also in ordinary transplanted tumors; the frequency, however, varies according to the variety of cancer used for inoculation.

A retrogression of cancer is a very rare occurrence in spontaneous tumors which did not originate as a result of inoculation. Here, it is very much more unusual than in the case of transplanted tumors. But even in man a few cases have been observed, in which undoubtedly cancer began to retrograde spontaneously and a cure resulted. If we examine such retrograding cancers under the microscope we notice that cell proliferation may continue for a long time, notwithstanding the reduction in size of the tumor, and it is even possible to obtain a new growth from such a retrograding cancer if we inoculate into other individuals. But on the whole, and especially in certain varieties of such retrograding tumors, the cells have markedly lost in vitality, and if used for inoculation are less favorable to the development of large tumors.

All the characters of tumor cells that we have descrribed thus far do not sharply distinguish cancer from ordinary tissue cells; in fact, our considerations have been based on the supposition that they still retain the properties of ordinary tissue cells. And this is indeed the case. That cancer cells exert still some of the functions of the organs from which they are derived, can be demostrated in various ways. To cite one example that illustrates this fact especially well: It is known that the thyroid gland of man has certain functions which it performs through what is known as an internal secretion; the gland manufactures a substance that is probably discharged into the circulation and the presence of which is necessary for the preservation of health. After the complete removal of the thyroid certain characteristic diseases appear. Now, there is a case on record in which it could be proved that after removal of the thyroid which had become cancerous, through operation, a secondary metastatic nodule of the cancerous thyroid, a nodule, therefore, that itself consisted of cancerous tissue, still produced that internal secretion and prevented the appearance of those symptoms that invariably follow the removal of the gland.

If cancer and ordinary tissue cells are so similar, in what respects do they differ? Cancer cells differ from ordinary tissue cells from which they are derived, in the first place through their increased energy of growth, and, secondly, through their power to invade and infiltrate other tissues. And, again, both of these properties, as such, are not absolutely characteristic of cancer. We have means of stimulating the growth of ordinary tissue cells to such an extent that for a certain period to time it may in intensity even exceed the growth of cancer cells. A relatively slight increase in proliferative power is, for instance, noticed in wound healing, where the epithelium and the connective tissue grow into the wound until the defect has been filled. A much more striking method of causing a very pronounced tissue proliferation has recently been discovered. It has been found that a certain organ produces at certain intervals a specific substance that unites with the connective tissue cells of another organ. This chemical substance renders those connective tissue cells extraordinarily sensitive to various mechanical stimuli. It sensitizes these cells, as we may express it. Contact with a foreign body causes such sensitized cells to grow enormously and within a few days they reach the size of a tumor. But after a relatively short period, this proliferation ceases again simultaneously with the cessation of the internal secretion which called forth its growth. Cancerous growth differs from such proliferation in being constant. The increase in proliferative energy is not temporary, but continuous; and such a continuous proliferation we have not yet been able to produce at will experimentally, and this is one of the reasons why the cancer problem cannot yet be regarded as solved. Temporary tumors we can produce at will—but not real cancers, which grow permanently.

The second characteristic property of cancerous growth is its power to infiltrate and to destroy the surrounding tissue. But even this power is not an absolutely unknown quality. During embryonic development certain cells of the outer layer of the embryo normally penetrate into the surrounding tissue to which they are attached and which nourishes them. Here again we have to deal with a passing phenomenon, while in cancer the infiltrative growth is permanent.

Cancer cells differ, therefore, from other cells in so far as they have constantly certain characteristics which other body cells possess, if at all, only temporarily. And one side of the cancer problem is to find means of producing such an increased energy of growth and an infiltrative growth permanently. Under certain conditions we have, however, succeeded in producing experimentally a new tumor. If we inoculate an epithelial cancer, a carcinoma, into a mouse or rat, we have observed, in a certain number of cases, that there developed in the inoculated mice, not only a carcinoma, but also a connective tissue tumor, a sarcoma, and both these tumors could then be separately propagated in other individuals. This remarkable fact has been observed in a number of tumors and at various periods after the inoculation, and it is probably due to a stimulating influence of unknown nature which the cancerous cells exert upon the surrounding connective tissue. Similar observations have been made in man. A person at first suffered from epithelial cancer of the thyroid and was operated on twice. In neither operation was it possible to excise the tumor completely; a few cancerous cell nests remained, and gave rise to a recurrence and to secondary nodules (metastases) in other organs. In the recurrent tumors and in the metastases, however, the epithelial cancer, the carcinoma, was gradually replaced by a connective tissue cancer, a sarcoma. Here the explanation is probably similar to the one given in the case of the experimental work: The cancerous epithelium transmits to the surrounding connective tissue a certain stimulus of growth. Such an occurrence explains probably also the fact that in certain cases we find in man and in animals in the same organ simultaneously two cancers, a carcinoma and a sarcoma; one of the two tumors being at first the only cancer present but causing secondarily the second cancer, the sarcoma, or the carcinoma, to be produced by the normal tissue. But even in the experiments just mentioned, we cannot be entirely satisfied with our experimental results, inasmuch as we cannot produce such a transformation of normal connective tissue into sarcoma at will; it sometimes happens to take place, while at other times we do not succeed. There are here evidently some variable factors present which we do not yet recognize and control. Or we might cite certain tumors developing in man under the influences of the Roentgen rays. In this case, also, we evidently do not yet control all the variable factors, inasmuch as we have not yet been able to reproduce such a change at will in animals.

We have now followed the activities of cancer cells and we have studied their behaviour under different conditions. This, however, is only one side of the problem. Cancer is a struggle between a number of cells of a certain organism against the rest of the body. It is an insurrection, in which, we regret to say, the insurgents have so far been victorious in the large majority of cases. As in every other war there are two armies. Let us now observe very briefly the activities of the other side and see what efforts they make to resist the invading enemy. As we mentioned above, the resisting powers in individuals affected by spontaneous cancer are very slight, but sometimes it takes many years, at other times, a few months, before the battle is ended. That depends partly upon the virulence of the cancer cells. Some varieties of cancer have much greater propagating and invading powers than others; partly it depends on the resistance offered by the patient. And here it has been observed that cancers frequently progress much more rapidly in vigorous young persons than in old individuals. Thus far our investigations into reactions taking place in the individual in which the cancer developed spontaneously, have necessarily been incomplete, although to some important observations we shall have occasion to refer later on. We are in a much more favorable condition, when he wish to study in animals the behaviour of the organism in cases of inoculated tumors. And here some very important facts have been disclosed.

In the first place, many animals resist successfully the growth of particles of tumor with which they have been inoculated. These individuals are naturally immune. Such natural immunity may in part depend on the constitution of the body fluids, the blood and the lymph, not favorable to the growth of the implanted cancer cells or it may be due to the reaction of the host cells which surround and invade the foreign cancer tissue. In a similar way, after transplantation of normal skin into a nearly related species in which the skin cannot grow successfully—for instance, after transplantation of guinea-pig skin into a rabbit—we notice that during the first week after transplantation, the epithelial cells of the guinea-pig skin may proliferate to a slight extent, but soon the growth ceases and the transplanted cells die. In a similar way the transplanted cancer cells may grow during a short period of time in an animal that is naturally immune, but here also the cells die very soon. Sometimes, however, an animal which resists one or two inoculations may not retain its immunity indefinitely but may succumb later to a successful inoculation.

Other animals are not naturally immune against the growth of inoculated tumors, but they can be made to become immune through experimental means. This can be done for instance, by inoculating an animal with cancer material of experimentally decreased virulence. As we have stated before, tumor cells that before inoculation had been exposed to a moderate degree of heat in many instances grow after transplantation, but after some time the growth ceases and then the tumor retrogrades. Now, it has been shown that such animals, in which the tumor has retrograded, have thereby become immune against cancer growth. In most cases they cannot be inoculated successfully a second time with particles of cancer previously not heated and therefore retaining their full virulence. Those animals that have been inoculated with heated material and in which the cancer cells of decreased virulence did not give origin to a temporary tumor formation, have not become immune through such inoclation, or at best have gained only a very slight degree of immunity. We see, therefore, that the actual growth of the tumor cells causes a reaction in the body of the host that leads to the mobilization of those forces that enable the organism to resist successfully a second attack, and that even induces after an initial period of growth the retrogression of the tumor. In a similar way it has been found that an immunity against pathogenic bacteria can, in certain cases, more easily be accomplished through the injection of living, than of previously killed, bacteria. That such defensive reactions take place in the animal in which a tumor is growing, is also evidenced by the fact that in certain varieties of cancer an animal in which a cancer is growing cannot be inoculated a second time with the same kind of tumor. Other means have been discovered by which it is possible to immunize animals against a successful inoculation with cancer. The methods used are again similar to those applied in infectious diseases. In order to immunize man against smallpox he is inoculated with an attenuated virus, the vaccine. If we inoculate mice with particles of normal mouse organs or with certain cancers that do not grow after transplantation, the animals thus treated become immune against inoculation with virulent tumor in a very large number of cases. This is due to the fact that cells in the normal organs and in the tumors have certain chemical constituents in common, which, after injection, are absorbed and give rise to defensive reactions that protect the animals against the growth of cancer cells.

In the case of diphtheria and other infectious diseases we can immunize animals by the repeated injection of the bacilli or their toxins, and afterwards we can transfer the immunity thus produced to other individuals of the same or other species. In this case the immunity present in the animals injected with bacteria or their toxins is due to the production of new substances, the anti-toxins or the anti-bacterial substances, and these substances can be transferred from one animal to another in a manner similar to that in which ordinary chemical substances can be introduced into an animal. The methods employed in diphtheria have been used for procuring curative blood sera against cancer. Many attempts have been made to produce substances which might be able to destroy the tumor cells and thus to procure a cure. For this purpose human cancer tissue has been injected into animals with negative results so far as the curative properties of the serum was concerned. In other experiments rabbits have been repeatedly injected with the cancer of mice; but the rabbit-serum thus obtained did not possess when injected into mice and properties decisively either curative or preventive. Whether the serum of animals that after recovery from a transplanted growth have become immune against a second inoculation has anti-cancerous action, injurious to the life of the cancer cells, has not yet been fully decided. Notwithstanding these, in part unsuccessful, attempts we thus see that the organism under various conditions is able to react against the invading cancer cells, and this fact encourages us to look forward with hope to the result of further investigation.

Let us now leave the field of theoretical research into the nature of cancer and into the life of the cancer cells, and return for a short time to the point of view of the physician, and learn what he can teach us regarding the cause and the cure of cancer.

If we inquire into the cause of tumors, several established facts stand out prominently. In the first place, external factors are of extreme importance in the etiology of cancer. In very many instances we notice that cancer is the result of chronic irritation of various kinds. Cancer of the lip is almost invariably found in places where chronic irritation due to smoking has injured the lip. In India and Ceylon, carcinoma of the mouth is not uncommon among women who are accustomed to chew the betel nut. In Kashmir, it is customary for the natives to carry small stoves that press against the skin of the abdomen and frequently burn it. As a result of such repeated burns, cancer develops in the skin of the abdomen in a relatively large percentage of cases among the inhabitants of Kashmir. Cancer of the gall bladder is frequently preceded by gallstones, which irritate the ball bladder, and cancer of the stomach develops frequently as a result of an ulcer of the stomach. In a similar way, chemical irritants of various kinds are liable to produce cancer. Thus, in chimney sweeps and in tar and paraffin workers cancer is relatively frequent, and in aniline workers cancer is found in certain organs. Furthermore, it occasionally develops in persons who take arsenic over a long period of time, for the purpose of curing certain kinds of diseases. We have mentioned before that it develops frequently in physicians who have exposed their skin to the action of the Roentgen rays without being protected by a screen. Thus, we find that a large proportion of earlier Roentgen ray technicians developed carcinoma of the hand and of the arm. Light may act in a manner similar to Roentgen rays in persons especially sensitive to the influence exerted by the short wave light rays. Thus in sailors, carcinoma of the skin develops occasionally. Even a single injury may sometimes be followed by cancer; and in this case it is usually a connective tissue cancer, a sarcoma that follows traumatism.

There are other factors of importance. During embryonal development certain cells or tissues or parts of organs may become misplaced. Now it has been observed that such misplaced embryonal rests may give rise to benign, tumor-like structures; and it has furthermore been observed that parts of such benign tumors undergo a transformation into cancer in a certain percentage of cases. Why it is, that such embryonal malformations are especially liable to become cancerous, we cannot state at the present time. Experimentally we have not been able to produce a cancer through misplacement of embryonal tissue.

It is likewise doubtful what part heredity plays in the formation of cancer. There can be no question that many cases have been found in which numerous members of a single family have fallen victims to cancer, and that such a tendency could be noted through several generations. Especially well known is the case of the family of Napoleon Bonaparte. In many other cases, however, no indication of hereditary transmission is noticeable, and at present we must leave the question as to the importance of hereditary factors undecided, although the weight of the evidence seems to me to point to the conclusion that heredity may play a part in the causation of cancer. To cite an instance where hereditary factors may indirectly be important: It is well known that certain pigmented moles are frequently transmitted from one generation to another, and it is certain that such pigmented moles may give rise to pigmented cancer of the skin of a very malignant type. In this case there is no doubt that indirectly heredity plays a role in the etiology of cancer.

One possible etiological factor that has led to more discussion than any other problem connected with cancer has still to be mentioned. I refer to the possible part played by parasites of various kinds. It is well known that in plants various fungi and insects, through chemical or mechanical stimulation, are able to call forth the production of simple or complicated galls, which in some respects resemble tumors. We also know that in animals various parasites can cause a proliferation of various tissue cells. But such tissue proliferations, in which parasites are found, differ, as far as we know at the present time, from the real tumors. In cancer no definite parasite has been found the presence of which is so regular or so specific that it could be recognized as the cause of the disease. On the other hand, certain facts could best be explained by the presence of a living agency calling forth the cancerous tissue proliferation. To cite one of the most important facts: In certain cases cancer in animals has been found to be endemic; it occurs very much more frequently in certain places and in certain families than in others. But this endemic occurrence of cancer might also be due to family or hereditary conditions or to a common influence of food. In the cases known so far, the infective cause of such an endemic occurrence has not yet been proved. Future investigation, however, must decide these questions.

A few words may be added in regard to the treatment of cancer. In the beginning, cancer is in the large majority of cases a strictly localized disease, and by a very early, thorough operation a definite cure may be attained. At later stages an operation frequently fails to eradicate the disease. In certain superficially situated cancers Roentgen or radium rays may lead to a cure, but they usually fail in cancers that are situated in the deeper tissues. Quite recently some excellent results have been achieved in advanced cases of carcinoma by the injection of the peritoneal fluid obtained from another patient suffering from cancer. It appears that in cancer reactions may take place in the patient that lead to the production of immune or sensitizing substances. It is, however, as yet much too early to make definite statements as to the mode of action of such fluid. Our experimental studies certainly have demonstrated the existence of such reactive processes in the individual affected by cancer as lead to a cure in a certain number of cases. I believe that we may look into the future hopefully and, perhaps very soon, but certainly sooner or later, we shall be able to control the conditions leading to the development of cancer; furthermore, that we shall be able to find more powerful curative agencies than we possess at the present time. We may, however, be sure that the most rational treatment will be based on purely scientific investigations into the ultimate nature of that kind of exaggerated tissue growth which we call cancer.